MOLECULAR AND CELLULAR MECHANISMS LEADING TO SIMILAR PHENOTYPES IN DOWN AND FETAL ALCOHOL SYNDROMES

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Down syndrome (DS) and Fetal Alcohol Syndrome (FAS) are two leading causes of birth defects with phenotypes ranging from cognitive impairment to craniofacial abnormalities. While DS originates from the trisomy of human chromosome 21 and FAS from prenatal alcohol consumption, many of the defining characteristics for these two disorders are stunningly similar. A survey of the literature revealed over 20 similar craniofacial and structural deficits in both human and mouse models of DS and FAS. We hypothesized that the similar phenotypes observed are caused by disruptions in common molecular or cellular pathways during development. To test our hypothesis, we examined morphometric, genetic, and cellular phenotypes during development of our DS and FAS mouse models at embryonic days 9.5-10.5. Our preliminary evidence indicates that during early development, dysregulation of *Dyrk1a* and *Rcan1*, cardinal genes affecting craniofacial and neurological precursors of DS, are also dysregulated in embryonic FAS models. Furthermore, Caspase 3 was also found to have similar expression in DS and FAS craniofacial neural crest derived tissues such as the first branchial arch (BA1) and regions of the brain. This may explain a developmental deficit by means of increased apoptosis. We are currently investigating the expression of pAkt, a protein shown to be affected in FAS models, in cells located in these same craniofacial and neurological regions in DS models. Recent research shows that *Ttc3*, a gene that is triplicated and shown to be overexpressed in our DS mouse model, targets pAkt in the nucleus affecting important transcription factors regulating cell cycle and cell survival. While Akt has been shown to play a role in neuronal development, we hypothesize that it also affects similar cellular properties in craniofacial precursors during development. By comparing common genotypes and phenotypes of DS and FAS we may provide common mechanisms to target for potential treatments of both disorders.

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